

R E M A R K S

Claims 1, 3-7, 10, 12-17, 19-21, 23-26, and 38-39 are pending in the application. Claims 2, 8-9, 11, 18, 22, and 27-37 are canceled, without prejudice. Claims 38 and 39 are new dependent claims.

Claims 1, 3-10, 12-17, 19-21, and 23-26 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. Claims 1, 3-6, 12-15, 17, 23, 24, and 26 have been rejected under 35 U.S.C. §102(b) as allegedly anticipated by Heidari et al., *Veterinary Immunology and Immunopathology*, 81:45-57, published August 2001 (“Heidari”). Claims 1, 3-10, 12-17, 19-21, and 23-26 have been rejected as allegedly obvious under §103 from Heidari in view of Carrio and Viilaverde, *Journal of Biotechnology*, 96:3-12, published June 13, 2002 (“Carrio”).

Claims 1 and 26 are amended herein to more particularly point out and distinctly define what is claimed. Support for the amendments may be found throughout the specification and claims as originally filed, for example, in canceled Claim 2, and on page 8, from lines 5-27. Claims 38 and 39 are new dependent claims. Support for the new claims may be found in previously presented Claim 30 and originally filed Claim 31, as well as throughout the specification. No new matter is added into the case by any of these amendments.

All objections and rejections are respectfully traversed. Reconsideration and favorable action are requested in light of the forgoing amendments and these remarks.

A. Claims 1, 3-7, 10, 12-17, 19-21, and 23-26 are Definite.

Claims 1, 3-10, 12-17, 19-21, and 23-26 are said to be indefinite under §112, second paragraph. Independent Claim 1 is directed to a process for the making a biologically active protein, and Claims 3-10, 12-17, 19-21, and 23-26 depend, directly or indirectly, from Claim 1.

It is alleged that Claim 1 omits essential elements. While Claim 1 is believed to be section 112-compliant, the claim is amended herein to more distinctly define and particularly point out the claimed subject matter, and the relationships among the recited elements and steps. Support for the amendment can be found throughout the specification and in the claims as originally filed. For example, Claim 1 is amended to clarify the process steps as taught in the paragraph bridging pages 5 and 6 of the specification, on pages 15 and 16, and in examples 1-12 on pages 16-34. No new matter is added into the case by the amendments. It is believed that the

present amendments overcome the rejection.

Claim 1 is also said to be vague and indefinite for reciting the terms “induction mode”, “principle of performing the fermentation, and “an agent capable of causing stress”. This is not understood. The recited terms are defined in the specification and in the claims as originally filed. For example, pages 11-14 describe the recited terms with sufficient clarity that one of ordinary skill in the art reading the application would plainly know the metes and bounds of the claims vis-à-vis these limitations. It is further made clear from the examples that regulation of one or more of the recited parameters increases the amount of substantially correctly folded protein precursor in the inclusion bodies of the cells of the cultivated organism.

Accordingly, Claim 1 as amended is sufficiently definite under 35 U.S.C. §112, and a person of ordinary skill in the art reading the claim would be well apprised of the metes and bounds of the claimed subject matter.

Claims 3-7, 10, 12-17, 19-21, and 23-26 are said to be indefinite for depending from an allegedly indefinite base claim. However, it has been shown that the base claim is not indefinite. The dependent claims should therefore also be deemed compliant with §112 since their alleged §112 problems were said to stem from the fact of their dependancy. Accordingly, reconsideration and allowance of Claims 1, 3-7, 10, 12-17, 19-21, and 23-26 are hereby respectfully requested.

B. Claims 1, 3-6, 12-15, 17, 23, 24, and 26 Are Not Anticipated By the Cited Reference.

Claims 1, 3-6, 12-15, 17, 23, 24, and 26 are said to be anticipated by Heidari. With all due respect, this argument is not well taken. It is a well-known principle of patent law that in order for a reference to anticipate a claim according to the law, it must describe each and every limitation of the claim in its four corners. If a single limitation is missing, then the reference does not anticipate the claim.

Heidara falls short of disclosing all the limitations of the subject claims. In particular, Heidari lacks any disclosure of the claim 1 step of solubilizing the protein precursor from the inclusion bodies under non-denaturing conditions. This is evident from the fact that the present application teaches that 2% N-lauoyl sarcosine is a strong denaturant (paragraph bridging pages 2 and 3). Heidari uses 2% solution of sarkosyl (N-lauroyl sarcosine) to solubilize proteins (page 47, under 2.4). Therefore Heidari fails to teach at least the claimed step of solubilizing the

including bodies under non-denaturing conditions and, as a result, cannot properly be said to anticipate Claim 1.

Heidari also teaches the steps of denaturation, oxidation, and renaturation of the protein in order to allegedly produce a biologically active protein. The invention called for in claim 1 advantageously avoids these steps by cultivating the organism in such a manner that a biologically active protein can be recovered without any denaturation and renaturation steps. Accordingly, Heidari is further shown to be deficient in teaching, disclosing, or suggesting the step of solubilizing the protein precursor from the inclusion bodies under non-denaturing conditions (i.e., by using a solvent at non-denaturing concentrations).

Since Heidari does not disclose all the limitations of Claim 1, Heidari cannot lawfully be said to anticipate the claim. And since the base claim is not anticipated by Heidari, the dependent claims must also patentably distinguish over the cited reference. Hence, reconsideration and allowance of Claim 1, and dependent Claims 3-7, 10, 12-17, 19-21, and 23-26 are hereby respectfully requested.

C. Claims 1, 3-7, 10, 12-17, 19-21, and 23-26 are Patentable Over the Cited References.

Claims 1, 3-7, 10, 12-17, 19-21, and 23-26 are said to be obvious over Heidari in view of Carrio. It is submitted that this rejection is also not well taken because, among other things, a reference or combination of references cannot properly be said to render a claim obvious when it does not contain all of the elements or limitations in the claim. Plus, it must be shown that a person of ordinary skill in the art would have found it “obvious” to put those elements and limitations together in the manner called for in the claim. The rejections here fail on both counts.

Claim 1 is an independent claim from which the all remaining claims depend. Claim 1, as amended, is directed to a process for the production of a biologically active protein. The protein is expressed as a heterologous protein in inclusion bodies in an expression system comprising cells of a cultivated organism. One or more cultivation parameters are regulated to increase the proportion of substantially correctly folded protein precursor present in the inclusion bodies in the cells. The inclusion bodies are then isolated from the cells, optionally washed, and the substantially correctly folded protein precursor is then solubilized from the inclusion bodies

under non-denaturing conditions (i.e., in a non-denaturing solution). The biologically active protein is then purified from the solubilized substantially correctly folded protein precursor.

The present claims are patentable over Heidari for at least the reasons mentioned in part B above. In an attempt to remedy the deficiencies of Heidari, the Examiner resorts to Carrio, but to no avail. The combined references do not disclose or suggest the subject matter of Claim 1. Specifically, Carrio, like Heidari, fails to teach, disclose, or suggest solubilizing a protein precursor from the inclusion bodies under non-denaturing conditions, as claimed.

However, even if Carrio and Heidari provided all of the elements of the present claims, which they do not, the present claims **still** would not be obvious from the combined references. According to the MPEP, the teachings of the references must be considered in their totality as to what might be suggested to one of ordinary skill in the art (MPEP 2141.02). Carrio makes a point of repeating, several times through the article, that protein solubility and inclusion body formation are generally unpredictable (page 4, second column). Carrio further states that different methodologies must be adapted to particular polypeptides in order to obtain soluble protein *in vitro* (page 5, first column). This high degree of unpredictability in the art serves as further evidence for the nonobviousness of Applicants' claims. A person of ordinary skill in the art would have no motivation to attempt to produce Applicants' claimed subject matter from the cited references, much less any reasonable expectation of success that any such imaged combination would be effective.

Furthermore, Carrio teaches basically the same method of protein extraction as Heidari, namely, a process involving denaturation and renaturation (refolding) of the protein being extracted (page 5, first column). Given this redundancy, there is no reason to combine them in the first place, and no teaching, disclosure, or suggestion in the references that a biologically active protein could be recovered from inclusion bodies without undergoing denaturation/renaturation. Therefore, a person of ordinary skill in the art reading the references would have no reasonable expectation for success at arriving at the present claims by combining the references in the manner suggested in the office action.

Claims 3-7, 10, 13-17, 19-21, and 23-26 depend from Claim 1 and add further elements and limitations thereto, also not disclosed in or obvious from the cited reference. According to the MPEP, if a base claim is allowable, then all of its dependents are also allowable. Since the

aforementioned claims all depend from Claim 1, which has been shown to be patentable over the references, then the dependent claims should also be allowable. Reconsideration and allowance of Claims 1, 3-7, 10, 13-17, 19-21, and 23-26 are hereby respectfully requested.

CONCLUSION

Finally, it is advised in the Office Action that if claim 3 is found to be allowable, then claim 4 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. Since claim 3 is believed to be allowable, upon receipt of a Notice of Allowance, Applicants represent that they will file a further amendment requesting cancellation of claim 4.

Also, upon the allowance of claim 1, rejoinder of the non-elected species of claim 3 will be requested.

Further, in light of the above remarks, consideration and allowance of new dependent claims 39 and 39 are also respectfully requested.

Applicants respectfully submit that a full and complete response to the office action is provided herein, and that the application is now fully in condition for allowance. Action in accordance therewith is respectfully requested.

In the event this response is not timely filed, Applicants hereby petition for the appropriate extension of time and request that the fee for the extension along with any other fees which may be due with respect to this paper be charged to our Deposit Account No. 12-2355.

Respectfully submitted,
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